those of guanine nucleotide dissociation inhibitors, which directly block Rho activation (Anastasiadis et al., 2000), suggesting that p120-catenin can affect Rho in multiple ways. Moreover, although the current report implies a key role for cadherin in the p120-catenin/p190 RhoGAP mechanism, p120-catenin can also inhibit Rho signaling by a cadherin-independent mechanism (Yanagisawa and Anastasiadis, 2006). So clearly we have much more to learn about the interactions of p120-catenin and Rho.

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ER Targeting Signals: More than Meets the Eye?

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The signal sequences that target newly synthesized proteins to the endoplasmic reticulum are highly variable; however, the functional significance of this diversity has remained obscure. In this issue, Kang et al. (2006) report that variability in signal sequences allows the cell to selectively regulate the translocation of proteins into the endoplasmic reticulum in a substrate-specific manner.

Since the discovery of signals that target proteins to the endoplasmic reticulum (ER), it has largely been assumed that their sole function is to direct nascent polypeptides to the ER translocation machinery. Besides being hydrophobic, there appeared to be few constraints on the precise sequence of these targeting signals (von Heijne, 1985, Kaiser et al., 1987). However, a growing body of evidence suggests that the exact nature of individual signals can have major physiological consequences beyond the fundamental targeting step. Thus, ER signal sequences may have specific posttargeting functions, such as the regulation of gene expression (Martoglio et al., 1997) or viral assembly (York et al., 2004). Paradoxically, many proteins appear to use signal sequences that are relatively inefficient for targeting per se (Levine et al., 2005). In this issue, Kang et al. (2006) suggest that such inefficient signal sequences may have a direct role in regulating the biosynthetic load in the ER during conditions of stress.

Various experimental and physiological causes of ER stress are known, including disruption of redox status, perturbation of calcium ion homeostasis, and the synthesis of mutant proteins. These typically compromise the chaperone-mediated protein folding capacity inside the ER, often causing a potentially harmful accumulation of misfolded proteins within the ER lumen. Eukaryotic cells have several mechanisms to limit the build up of such misfolded proteins. One mechanism acts to increase ER folding capacity by upregulating the expression of many luminal chaperones via a signaling network referred to as the unfolded protein response (Rutkowski and Kaufman, 2004). Another mechanism removes misfolded proteins that could otherwise saturate the folding machinery with nonproductive interactions, via the ER-associated degradation pathway. In this pathway, terminally misfolded proteins are transported back across the ER membrane into the cytosol and degraded by the proteasome (Meusser et al., 2005). A third strategy is to reduce the volume of newly synthesized proteins entering the ER that

involves a global attenuation of protein synthesis by inhibition of the translation machinery. It is now clear that the selective degradation of a subset of mRNAs localized to the ER also contributes to reducing the ER workload during stress (Hollien and Weissman, 2006). The study by Kang et al. (2006) suggests yet another means to selectively decrease the quantity of proteins entering the ER and is based on the stress-induced inhibition of protein translocation. They term this new mechanism "pre-emptive quality control" because it triages proteins before they engage the conventional quality control machinery that monitors protein folding inside the ER lumen. The most remarkable feature of this new pathway is that its selectivity is based upon differences between apparently generic ER signal sequences. Thus, although many proteins are prevented from entering the ER during stress, proteins that can specifically combat the effects of such stress are still efficiently transported. Using a cellular model of ER stress, Kang et al. (2006) show that the molecular chaperone BiP continues to be efficiently translocated into the ER during stress, whereas typical cargo proteins destined for the plasma membrane or secretion, such as the prion protein (PrP), are refused entry. By making chimeric proteins, they demonstrate that the ability of stress to inhibit the translocation of PrP into the ER is dependent upon its signal sequence. At present, the precise difference between signal sequences—those that can be regulated (SS^{REG}) and those that are constitutive (SS^{CON})—is not readily apparent. Likewise, the molecular basis by which the ER translocation machinery might discriminate between them remains to be established. Using in vitro approaches, Kang et al. (2006) show that ER luminal factors facilitate protein translocation and demonstrate that the signal sequence dictates the extent to which these are required.

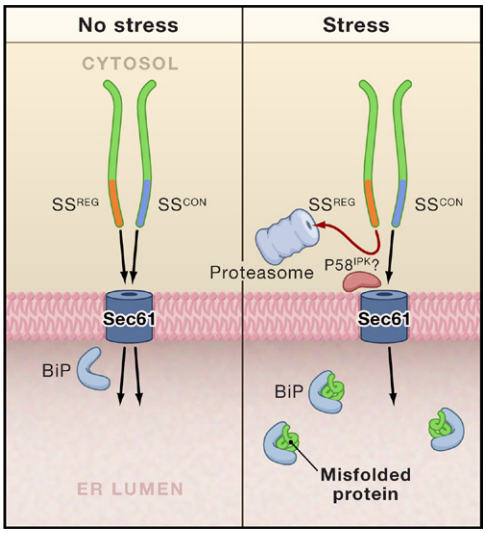

Figure 1. Reducing the Secretory Load during ER Stress

In the absence of stress, nascent polypeptides are translocated into the ER lumen via the Sec61 translocon. Under these conditions, there is an ample amount of the molecular chaperone BiP available within the ER lumen to facilitate the translocation of nascent chains possessing a signal sequence that can be regulated (SS^{REG}). During ER stress, misfolded proteins accumulate in the ER and bind to luminal chaperones such as BiP, reducing their availability. As a result, polypeptides carrying the SS^{REG} signal fail to be translocated and are instead targeted for degradation, possibly via the actions of $P58^{IPK}$. In contrast, the translocation of proteins possessing a constitutive signal sequence (SS^{CON}), which is less dependent on BiP, continues. This signal sequence specific attenuation of translocation into the ER lumen selectively decreases the amount of cargo entering the ER during stress without impeding the entry of proteins that can counteract the effects of the stress.

Thus, polypeptides possessing the SS^{REG} of PrP are highly dependent on luminal factors, whereas those with SS^{CON} are not. If one assumes that the important luminal factors are chaperones like BiP, which has reduced availability during conditions of ER stress, then this provides an elegant mechanism for the selective inhibition of protein translocation into the ER (Figure 1).

What is the fate of the selectively nontranslocated polypeptides? Although Kang et al. (2006) clearly show that these precursors are delivered to the ER membrane—presumably via the conventional signal recognition particle dependent pathway—the precise point at which their entry into the ER is blocked is not clear. Thus, it remains possible that nascent chains possessing SS^{REG} signals are rapidly rejected by the ER translocon and immediately diverted into the cytosol for degradation by the proteasome. Alternatively, the rejected precursor polypeptides may partially engage the translocon and require active extraction before their degradation. Strikingly, a potential mechanism for exactly this purpose has been independently discovered by Oyadomari et al. (2006) earlier this year. They show that the protein $P58^{IPK}$, which is induced during the unfolded protein response, contributes to the extraction of nascent polypeptides from the ER translocon, enabling their subsequent degradation by the proteasome. $P58^{IPK}$ is proposed to act as an adaptor between the ER translocon and cytosolic Hsp70, which could potentially provide the driving force to extract stalled polypeptides. This pathway appears to function primarily under conditions of ER stress, and compelling evidence is provided for the physiological importance of $P58^{IPK}$ in protecting cells from ER stress in vivo. Whether $P58^{IPK}$ plays any role in the inhibition of translocation observed by Kang et al. (2006) remains to be seen.

What is the particular advantage of this additional layer of protection mediated by the signal sequence against ER stress? Given that this response is both remarkably swift and readily reversible, it could enable cells to respond to transient perturbations in ER homeostasis, thereby quickly re-establishing the status quo without requiring the activation of a full-blown unfolded protein response and its associated cellular consequences. In this way, it could provide a mechanism for self regulation that allows the ER to balance the amount of protein entering the lumen with the capabilities of its protein folding machinery. Furthermore, its selectivity seems tailored to prioritize the translocation of components that are particularly beneficial during ER stress by freeing up the translocation machinery for the import of proteins induced by the unfolded protein

response. Such major advances in our understanding of the individual pathways and components that maintain ER homeostasis after physiological and pathological challenges raises the fundamental question of precisely how these varied processes are coordinated to provide a coherent response in vivo.

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A Role for p130Cas in Mechanotransduction

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Focal adhesions are sites of contact between cells and the extracellular matrix. Sawada et al. (2006) now report that the mechanical stretching of cells forces p130Cas, an adaptor protein at focal adhesions, to undergo a conformational change. This change promotes phosphorylation of p130Cas by Src family kinases and the transduction of integrin-mediated signaling.

Physical interactions between cells and the extracellular matrix occur at focal adhesions, where integrins cluster and bind to the matix. A primary function of these cell contacts is to provide mechanical support and maintain tissue integrity. However, it has become increasingly apparent that focal adhesions also function as sensory and signaling organelles, which collect complex information concerning the chemical and physical nature of the extracellular matrix, integrate this information, and trigger appropriate cellular responses. Although it is well known that diverse matrices modulate cell morphology and fate, the molecular mechanisms responsible for these effects are still poorly understood. In this issue, Sawada et al. (2006) provide evidence that the sensitivity of focal adhesions to mechanical stimulation is mediated by stretching of the adaptor protein p130Cas, which enhances its phophorylation by Src family kinases. This, in turn, promotes the recruitment of p130Cas partners that promote cell migration by activating small GTPases, such as Rap1.

Mechanotransduction is an essential function of focal adhesions. For example, the cellular responses mediated by integrins require adhesion to a solid matrix and cannot be triggered effectively by binding to soluble matrix molecules (Discher et al., 2005). Mechanical stimulation affects the size and subcellular location of focal adhesions, as well as the activation of specific signaling events (Yoshigi et al., 2005). Moreover, the rigidity of adhesive substrates affects how cells attach, spread, polarize, and migrate (Discher et al., 2005). Mechanical signals can also be applied to the cell from the outside, such as by shear stress, direct mechanical manipulation of the cell, or stretching of the underlying substrate (Bershadsky et al., 2006).

The engagement of integrins by the extracellular matrix leads to the specific tyrosine phosphorylation of components of focal adhesions, such as focal adhesion kinase (FAK), paxilin, and the adaptor protein p130Cas. Because integrins do not possess an intrinsic enzymatic activity, these phosphorylation events are attributable to either activation of the Src/FAK pathway or to the inhibition of the corresponding phosphatases, such